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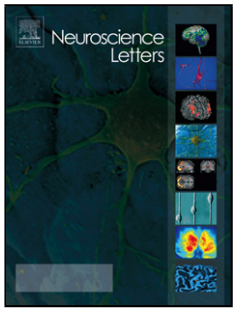

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The role of TRP channels in white matter function and ischaemia

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Highlights:

- TRP channels are heterogeneously expressed in glial cells.
- Here we summarise the suggested roles for glial TRP channels in physiology and pathology.
- More evidence is required to prove the existence and function of these glial TRP channels, and to determine how they contribute to pathology in stroke and other white matter diseases.

Abstract

Transient receptor potential (TRP) proteins are a large family of tetrameric non-selective cation channels that are widely expressed in the grey and white matter of the CNS, and are increasingly considered as potential therapeutic targets in brain disorders. Here we briefly review the evidence for TRP channel expression in glial cells and their possible role in both glial cell physiology and stroke. Despite their contribution to important functions, our understanding of the roles of TRP channels in glia is still in its infancy. The evidence reviewed here indicates that further investigation is needed to determine whether TRP channel inhibition can decrease damage or increase repair in stroke and other diseases affecting the white matter.

Keywords: TRP channels; astrocytes; oligodendrocytes; microglia; ischaemia; pathogenesis

Introduction

The central nervous system is composed of grey and white matter. The grey matter contains the neurons while the main function of the white matter is to support fast and energetically-efficient transmission of neuronal signals over large distances in the brain. To accomplish this, the white matter contains myelin provided by oligodendrocytes, which decreases the effective capacitance of the axonal membrane, so that less charge entry is needed to generate an action potential, oligodendrocyte precursor cells (OPCs), astrocytes and microglia. The importance of white matter function is highlighted by the symptoms that develop when white matter tracts are damaged in stroke [1].

It has long been realised that glial Ca^{2+} signalling is important for many glial cell functions including sensing and modulating the activity of local neurons (neuron-glial signalling; [2]), proliferation [3], migration [4] and myelination [5–7]. Furthermore, changes in local Na^{+} concentrations also have major physiological roles (reviewed by [8,9]). For these purposes the intracellular Na^{+} and Ca^{2+} concentrations are normally tightly regulated. When excessive increases

arise due to excitotoxicity, brain injury or stroke, this leads to pathological changes in cell functioning, mitochondrial damage, oxidative stress, the activation of proteolytic enzymes and eventually cell death by apoptosis or necrosis. In line with this, lowering the extracellular Ca^{2+} concentration during ischaemia protects against myelin damage [8] and loss of action potential propagation [9], and removing Na^{+} during ischaemia reduces damage to astrocytes [12]. Furthermore, astrocytes and microglia become "activated" when their intracellular Ca^{2+} concentrations increase during white matter damage [10,11].

A wealth of evidence shows that ionotropic glutamate receptors mediate a large proportion of white matter damage by allowing a large flux of ions into glial cells, and this has been reviewed elsewhere in this issue. Here we focus on new evidence suggesting that glial cell TRP channels also regulate ion concentrations in glia, and that activation of these channels can damage glia and modulate glutamate excitotoxicity. During white matter pathology, the local environment changes in a way that would activate many TRP channels (for example by decreasing extracellular pH or increasing the production of free radicals). As activation of TRP channels on glial cells would result in a large cation flux, which in turn can indirectly activate voltage-operated calcium channels by depolarising the membrane, we propose that TRP channels are important causes of white matter damage in pathology which could be targeted for therapy.

TRP channels in glial cells

There are 28 mammalian TRP channels separated into 6 sub-families: TRPC (where C denotes canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPP (poly-cystin), and TRPML (mucolipin). They share some structural similarity, but their functions are diverse and they display an incredible variety of activation mechanisms. These include activation by a multitude of ligands, physical stimuli (e.g. force and temperature), differing local ion concentrations and secondary messengers released via G-protein coupled receptors. There is a lot of evidence for the expression of TRPM, TRPV, TRPC and TRPA channels in glial cells, which we have reviewed here. However, the exact abundance and distribution of these TRP channels is still debated. While single cell mRNA analysis suggests that almost all TRP channels are expressed in subsets of glial cells [12], bulk sequencing studies that average the expression over large quantities of glia, have not found them. In the same manner, Shigetomi et al. [13], found that although Ca^{2+} imaging, anti-TRPA1 silencing RNA and pharmacology strongly suggested the presence of TRPA1 channels in astrocytes, they could not detect TRP protein by immunohistochemistry in the same cells. This discrepancy may exist because TRP channel expression is heterogeneous and not high enough to be measured as an average over many cells [12], and may also be because TRP channel expression is regulated by yet unknown factors which are changed between experiments, animals and disease models. Therefore, questions remain as to the degree, reason and timing of TRP channel expression, which we highlight below.

TRPC channels

The mammalian TRPC (canonical) family consists of seven members (TRPC1-7) that are organised into four groups depending on their sequence homology and functional similarities: TRPC1, TRPC2, TRPC3/6/7 and TRPC4/5 [14]. They are all non-specific cation channels with varying Ca^{2+}:Na^{+} permeability ratios [15], that can be activated by diacylglycerol (DAG), and thus Gq-coupled receptors generating DAG such as group 1 mGluR and muscarinic acetylcholine receptors, and possibly by mechanical stimulation [16]. In line with this, astrocyte TRPC1 is activated by glutamatergic or purinergic metabotropic receptors, or mechanical stimulation [17,18]. TRPC channels form heteromeric complexes that alter their biophysical properties and agonist profiles [19] making them difficult to identify pharmacologically. Despite this, TRPC1, 2, 3, 4 and 6 have been

found to be expressed by astrocytes [17,20–23], and TRPC3 [24] and TRPC6 [25] by microglia (reviewed by [26]). TRPC channels have also been found in the oligodendrocyte lineage, where TRPC1-6 are more highly expressed by OPCs and newly forming oligodendrocytes, and TRPC7 has greater expression in some mature oligodendrocyte populations [12]. Unlike astrocytes, the function of most TRPCs in oligodendrocyte lineage cells has not been explored to date.

TRPC1

Soon after the discovery of TRPC1 it was proposed to underlie store-operated Ca^{2+} entry (SOCE; Boulay et al., 1999). Stromal interaction molecule (STIM1 and STIM2) and Orai (1, 2 and 3) have since been held mainly responsible for this process, however convincing evidence still exists for a TRPC1-mediated component [28,29], and in oligodendrocyte precursor cells, small interfering RNA knockdown of TRPC1 reduces SOCE [30]. As TRPC1 forms heteromers with TRPC3, TRPC4 and TRPC5, it has also been postulated that a multimer may be responsible for astrocyte SOCE [31]. In line with this, TRPC3 inhibitors reduce SOCE in spinal astrocytes [23]. However in another study, knockout of TRPC1 or TRPC3 and TRPC6 did not affect SOCE in cortical astrocytes [20], and TRPC appears to have no role in SOCE in primary microglia [32]. Thus, the mechanisms responsible for SOCE in glial cells may be more complicated than supposed, and may differ between cell types [28].

Along with mediating SOCE in astrocytes, TRPC1 has the potential to regulate a huge variety of functions and to damage cells if they are excessively activated. Thus, astrocytes with TRPC1 genetically removed display increased migration *in vitro* and have increased injury-evoked astrogliosis *in vivo* [20]. Blocking TRPC1 with antibodies reduces glutamate release from cultured astrocytes [17]. This TRPC1-mediated control of glutamate release may regulate astrocyte-mediated effects on neuronal function during normal physiology [2], or influence ischaemia-evoked glutamate excitotoxicity in stroke.

TRPC2

TRPC2 is a pseudogene in humans but in rodents regulates the activity of the vomeronasal organ and the testis. In wildtype mice, only male mice mount other mice, usually a female. However in *Trpc2* -/- mice, both males and females mount other mice indiscriminately (reviewed by [33]). Only very low levels of TRPC2 have been found in astrocytes [20,22], microglia [32] and OPCs [12].

TRPC3

Like TRPC1, TRPC3 is activated by store depletion [28] and forms heteromeric channels with TRPC1 [20] and TRPC7 [34]. In contrast to TRPC1, TRPC3 dependent Ca^{2+} signalling in mouse cortical astrocytes increases proliferation and migration, and increases inflammation and oedema in stab wound injuries [20], and astrogliosis after ischaemia [35]. In line with that, TRPC3/C6/C7 knockouts are protected against ischaemia-evoked astrocyte apoptosis and have a reduced ischaemia-evoked infarct size [21], and ethyl-1-(4-(2,3,3-trichloroacrylamide)phenyl)-5-(trifluoromethyl)-1H-pyrazole-4-carboxylate (Pyr3), a TRPC3 antagonist, decreases astrogliosis in an *in vivo* intracerebral haemorrhage model [36]. Interestingly, immunolabelling for TRPC3 showed its expression mainly in oligodendrocytes [37], and therefore it may play a part in myelination as well as white matter pathology. Together, these data suggest that therapies targeted at TRPC3 may successfully inhibit white matter damage.

TRPC4 and TRPC5

Based on structural similarities, TRPC4 and TRPC5 are most closely related to TRPC1. These structural similarities aid in the formation of heterotetramers, and therefore tetramers involving TRPC1, TRPC4 and TRPC5 are common. This group of TRPC channels is activated following

stimulation by GPCRs of the Gq/11 family which couple to PLCβ, or receptor tyrosine kinases which couple to PLCγ [38]. Thus activation of the channels can be inhibited by inhibition of PLC [39]. Some variability in activation mechanism between different species is found, and has been extensively reviewed here [38].

TRPC4 and TRPC5 are expressed in astrocytes [17,40,41], with TRPC4 at discrete cell to cell contact sites [41]. There, TRPC4 with TRPC1 have been suggested to raise intracellular Ca^{2+} by mediating SOCE [40,41]. TRPC4 expression also increases in neurons in an *in vivo* model of ischaemia [42], however whether TRPC4 acts in a positive or detrimental manner is uncertain. The role of TRPC5 is unknown.

TRPC6

Immunoblotting, siRNA, knockout and Ca^{2+} imaging experiments suggest that TRPC6 is expressed in astrocytes [21,43,44] and microglia [25]. TRPC6 mRNA is also expressed in freshly dissociated oligodendrocyte lineage cells, but at a decreasing level as the cells mature [12]. A role for TRPC6 in inflammation and astrogliosis is supported by evidence that knockout of TRPC3/6/7, protects astrocytes against apoptosis during ischaemia *in vitro* and decreases the ischaemia-evoked infarct size in *vivo* [21]. As these channels are also involved in regulating vascular tone [45], this protection may also be due to changes in local perfusion. The relative contribution of the different TRPCs are unknown, and how their knockout affects other cell types has not been determined.

TRPC7

TRPC7 appears to be expressed in the human and rodent brain, but not in cultured astrocytes [44], or in optic nerve head astrocytes [22]. In contrast, transcriptome data from astrocytes in the whole brain suggest that TRPC7 may be expressed to some extent [46], and single cell transcriptome data from oligodendrocyte lineage cells suggest that TRPC7 is expressed by some myelinating and mature oligodendrocyte populations [12]. The functions of glial cell TRPC7 are unknown.

TRPM channels

The mammalian TRPM (melastatin) family consists of eight channels, TRPM1-TRPM8, that can be divided into four groups based on their sequence homology: TRPM1/3, TRM2/8, TRPM4/5 and TRPM6/7. They mediate a cation flux, but have a variable degree of Ca^{2+} permeability: TRPM4 and TRPM5 are Ca^{2+}-impermeable, TRPM3, TRPM6 and TRPM7 are highly permeable to both Ca^{2+} and Mg^{2+}, and the rest fit somewhere in between [15]. Like TRPC channels, almost all of the TRPM family (except TRPM8) have been determined to be expressed heterogeneously within different populations of glial cells [12,47–51]. However, our understanding of the functional role of TRPM channels in glial cells is limited.

TRPM1

TRPM1 is interesting as it is constitutively active and allows Ca^{2+} to enter cells that are still hyperpolarised. Its activity is inhibited by the activation of G-proteins, and mutations in TRPM1 can cause congenital night blindness [52]. Single cell transcriptome data suggest that TRPM1 can be expressed by oligodendrocyte lineage cells throughout their development [12], however the activation mechanism(s) and the function of TRPM1 in glial cells has not been explored.

TRPM2

TRPM2 is a chanzyme, made up of a channel fused with an enzymatic ADP-ribose pyrophosphatase domain, which is activated by ADP-ribose, NAD+, Ca^{2+} and heat. TRPM2 is

expressed by both astrocytes [46,50] and microglia [46], where it is thought to have a role in regulating immune cell function [53,54] and gliosis [49,55]. Importantly, TRPM2 knockout reduces ischaemia-evoked brain damage and activation of both astrocytes and microglia [55]. Its is not known whether this *in vivo* effect is increased by TRPM2 knockout from local neurons, which may indirectly activate glial cells. TRPM2 can be activated by reactive oxygen species and inflammatory cytokines, as well as ADP-ribose, and therefore is more likely to be activated during the reperfusion phase of ischaemia-reperfusion insults [55], when these substances are produced. Single cell transcriptome analysis suggests that this channel is more likely to be expressed in the oligodendrocyte lineage after differentiation [12], however transcriptome analysis of larger populations of glial cells suggest TRPM2 is expressed mainly by OPC populations [46], indicating that TRPM2 may be expressed in more OPCs at lower levels, and then increases its expression in only a proportion of the cells as they mature. Their function in oligodendrocyte lineage cells is unknown.

TRPM3

TRPM3 may have an important role in regulating glial cell Ca^{2+} concentrations, as it has been detected at relatively highly levels in astrocytes [46,51] and mature (or myelinating) oligodendrocytes [12,47,51], and can regulate SOCE in these cells in the rodent optic nerve [51]. TRPM3 has many splice variants, which may modulate its pharmacological profile [56,57] and these variants can be differentially expressed in the oligodendrocyte lineage [47]. TRPM3 is activated by D-erythro-sphingosine, pregnenolone sulphate and a decrease in extracellular osmolarity. As sphingosine is a major constituent of myelin, and TRPM3 is most greatly expressed around the time that myelination and myelin compaction occurs [47], TRPM3 may regulate the formation of the myelin sheath. TRPM3 also modulates glutamate release and mEPSC frequency in neonatal Purkinje cells [58]. Whether this mechanism is activated in glial cells or ischaemia, or whether it affects glial cells indirectly is unknown.

TRPM4/5

Though impermeable to Ca^{2+}, TRPM4 and TRPM5 are activated by intracellular Ca^{2+} and are therefore thought to play some role in controlling Ca^{2+} concentrations. Recent evidence also suggests that astrocytes express a sulfonylurea receptor 1 (SUR1)-TRPM4 and aquaporin-4 (AQP4) complex that regulates water movement and astrocyte swelling after injury [59]. TRPM4 is considered to form the pore of the SUR1/TRPM4 channel and SUR1 is a subunit of K_{ATP} channels. SUR1 is not believed to normally be expressed by glial cells, but is upregulated in astrocytes and microglia during stroke [60]. Whether TRPM4 ever forms this complex in oligodendrocytes is unknown, although TRPM4 RNA has been detected in subpopulations of oligodendrocytes and OPCs. There is no evidence for TRPM5 expression in glial cells.

TRPM6/7

Unlike other TRP channels, TRPM6 and TRPM7 have functional α-kinases that have structural similarity to protein kinase A [61] that are covalently linked to the C-termini. Both channels are constitutively active Mg^{2+}-permeable channels that are negatively regulated by intracellular Mg^{2+}, thus regulating $[Mg^{2+}]_i$ in the cells that express them [62]. There is only evidence for expression of TRPM7 in glial cells, which is thought to play roles in controlling migration and proliferation of astrocytes [46,63] and microglial migration and invasion [64]. TRPM7 is also found in OPCs [12], newly formed oligodendrocytes and endothelial cells [46]. Its function in these cells is unknown, but as it contributes extensively to pH-dependent neuronal damage during ischaemia, through Ca^{2+} overload, and generation of ROS [65,66], TRPM7 may also damage glial cells in the same situation.

TRPM8

TRPM8 has received a lot of interest, because it can be activated by low temperatures as well as menthol, eucalyptol and icilin [67]. It is expressed in primary afferent sensory neurons, but not thought to be expressed in the brain or by glial cells.

TRPV channels

There are six mammalian vanillin TRP channels that fit into four groups, TRPV1/2, TRPV3, TRPV4 and TRPV5/6 based on their sequence homology. All groups are Ca^{2+} selective however TRPV5/6 are the most highly Ca^{2+} selective channels in the TRP family [19]. They all can form homotetramers or heterotetramers.

TRPV1

TRPV1 is most highly expressed in peripheral sensory neurons, where extensive studies have found that it responds to physical and chemical stimuli such as noxious heat (>43°C), acidity, ROS, capsaicin and endogenous compounds such as arachidonic acid metabolites and endocannabinoids [19]. It is also expressed in the brain in neurons, astrocytes and microglia (for a review see [68]).

Due to the high Ca^{2+} permeability of TRPVs, and the ability of TRPV1 to be activated in hypoxia and inflammation, researchers have investigated its contribution to pathology. Interestingly, TRPV1 activation in glial cells is not always detrimental. On one side, TRPV1 expression in microglia has been suggested to disrupt mitochondria [69], increase ROS production [70,71] and mediate neuropathic pain [72]. Conversely, TRPV1 activation helps promote microglial-phagocytosis of damaged cells [73] and reduces microglia-induced oxidative stress [74,75].

TRPV1 has been shown to be expressed in astrocyte end feet [76] or thick processes [77], and to influence the migration of astrocytes when they become reactive [78]. However surprisingly, no change in the reaction of astrocytes or microglia was observed in after middle cerebral artery occlusion when TRPV1 was genetically removed or inhibited, despite there being a decrease in infarct volume and neurological deficits [79].

Whether TRPV1 is also activated in oligodendrocyte lineage cells is unknown, but this appears not to be the case for mature oligodendrocytes in the rat cerebellum, which do not respond when the TRPV1 agonist capsaicin is applied [80]. However, TRPV1 RNA is found in subpopulations of oligodendrocyte lineage cells [12] and TRPV1 immunolabelling is in alvear oligodendrocytes of the hippocampus [81]. Although there are many studies on the actions of TRPV1 in the brain, it not thought to be widely expressed there. More investigation will confirm whether it really is involved in these diverse functions.

TRPV2

TRPV2 can be activated by very high temperatures (>52°C), mechanical force, osmotic pressure and lipids [82]. Whether it is expressed by astrocytes is unclear, as it was not found in cultured human astrocytes [83] or rat retinal Muller cells or astrocytes [84], but was found in mouse cerebellar [85] and cortical [86] astrocytes. TRPV2 expression by cortical astrocytes in mice is thought to be enhanced during ischaemia, and blocking TRPV2 increases nerve growth factor-induced neuroprotection [86]. TRPV2 in microglia, like TRPV1, is thought to increase microglial phagocytosis evoked by cannabidiol (by 175%) [73]. It is also found at low levels in newly forming oligodendrocytes [12]. More work is needed to confirm the true extent of TRPV2 expression and its function.

TRPV3

TRPV3 is a rather underexplored TRP channel, activated by a variety of natural compounds such as carvacrol (which gives the smell of oregano), thymol, and eugenol [87]. It senses innocuous warm temperatures (22-40℃; [88,89]), and is inhibited by metabolites of omega 3 fatty acids, eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) [90]. It is widely expressed in the human body, mainly in keratinocytes and the brain. However, the role of TRPV3 in the brain is not known. We have no evidence suggesting that TRPV3 is expressed by either astrocytes or microglia, however *in situ* hybridisation of rodent cerebellum shows that TRPV3 is expressed in mature oligodendrocytes in the rat, but not in the mouse [80]. Although a TRP channel with properties similar to TRPV3 contributes to the Ca^{2+} influx occurring into rat cerebellar oligodendrocytes during ischaemia, a TRPV3 component could not be confirmed due to a lack of specific TRPV3 antagonists, and because only TRPV3 knockout mice and not rats are available [80].

TRPV4

TRPV4 has a role in regulating vascular function and the osmotic pressure in the brain [91]. It is highly expressed throughout the brain in glial cells [92–98], and TRPV4 mutations lead to neurological motor function disorders such as congenital distal spinal muscular atrophy, and a subtype of Charcot-Marie-Tooth disease [99]. Its activation is regulated by cell swelling and low extracellular pH. Therefore, TRPV4 may play an important role in glial cell pathophysiology associated with neurodegenerative diseases and ischaemia.

TRPV4 is expressed in the membrane of astrocytes, mainly on their processes, and its expression increases when they become reactive after ischaemia [93,97]. Astrocyte TRPV4 activation results in extracellular glutamate accumulation, which may contribute to glutamate excitotoxicity during ischaemia [97] or modulate synaptic function [100].

These results indicate that TRPV4 may be a useful therapeutic target in ischaemia, however TRPV4 antagonists may have an unwanted effect on neurovascular coupling. TRPV4-mediated Ca^{2+} signals in astrocyte end feet are activated by local neuronal activity, regulate astrocyte cell volume, and enhance the induced vasodilation [94]. These responses are augmented and propagated by Ca^{2+}-induced Ca^{2+} release [94].

TRPV4 also increases OPC proliferation with no effect on OPC differentiation [96], suggesting that TRPV4 activation may be a useful therapy for increasing OPC numbers in culture for cell transplantation, or briefly *in vivo*, after a bout of demyelination. These results are promising and highlight the fact that the role of TRPV4 in glial cells in the brain is under researched.

TRPV5/TRPV6

TRPV5 and TRPV6 are the most highly Ca^{2+}-selective TRP channels and are also interesting because of their possible link with neuroendocrine regulation. TRPV5 is primarily expressed in kidney epithelial cells, however it is also expressed at lower levels in the brain. Immunolabelling for TRPV5 indicates it is expressed in neurons and astrocytes [101]. In the arcuate nucleus, TRPV5 expression in astrocytes seems to be regulated by 17β-oestradiol or ischaemia, where it can cause a detrimental Ca^{2+} concentration rise [101].

TRPA1 channels

TRPA1 is the only member of the ankyrin family of TRP channels, so named because of the extensive number of ankyrin repeats located on its intracellular N-terminus [102]. It is best known as a sensor for environmental irritants and endogenous electrophilic compounds that are formed during oxidative stress [103] and evoke pain, cold, itch and inflammation [104], however it probably also has other undiscovered functions. In support of this assumption, along with decreased responses to peripheral pain models and temperature changes, global TRPA1 knockouts are hyperactive [105], and have sensory dysregulation, cognitive dysfunction, and motor deficits proposed to result from a decrease in myelination [106].

The role of TRPA1 and its expression in rodent glial cells is still contentious, as TRPA1 expression appears to be low [13,46], or only in scattered cells [12]. TRPA1 RNA was also not found in the optic nerve during studies of SOCE in glial cells [51]. However, using in situ hybridisation, we found low levels of TRPA1 RNA in most oligodendrocyte lineage cells [80]. Remarkably, TRPA1 knockout is also protective in the cuprizone model of demyelination [107].

In astrocytes, TRPA1 is thought to elevate the resting astrocyte Ca^{2+} concentration, which in turn modulates inhibitory synapse efficacy by controlling the membrane insertion of astrocyte GABA transporters (GAT-3) [13]. TRPA1-mediated Ca^{2+} signals are in discrete zones in the astrocyte processes [13], which can also be activated by amyloid-β oligomers [108], suggesting a possible role for astrocyte TRPA1 in the dysregulation of synaptic activity in Alzheimer's pathology.

As well as its role in inhibiting transporters, TRPA1 activation in cultured astrocytes can evoke the release of peptide hormones [109] and regulate long-term potentiation in the hippocampus via release of D-serine [110]. However, as in oligodendrocytes [80], TRPA1 expression in astrocytes appears to be too low to be observed with immunohistochemistry [13]. Although strong immunolabelling of TRPA1 in astrocytes and reactive astrocytes has been shown [107], this TRPA1 antibody strongly colocalises with GFAP even in TRPA1 knockouts (our unpublished observations). Therefore, the protective effect of TRPA1 knockout in the cuprizone model [107,111] may reflect protection from TRPA1 expression in either astrocytes or oligodendrocytes, or both.

Importantly, like some other TRP channels, TRPA1 expression is upregulated during inflammation [104,112,113], and therefore it may be important to measure TRPA1 expression in single cells during disease, to determine whether it plays a greater role than predicted by sequencing data from cells in healthy animals. Nonetheless, the evidence indicates that TRPA1 plays a role in glial cell regulation and homeostasis in the CNS, and that TRPA1 inhibition may be therapeutic in neurodegenerative diseases affecting the white matter.

Summary

The evidence reviewed here identifies many TRP channels that might regulate important glial cell functions and contribute to pathological signalling (Figure 1). Heterogeneity of receptor expression in glial cells exists within the same brain regions and this may explain why controversy exists in the literature over how white matter becomes damaged in disease. Although it is apparent that glutamatergic and purinergic receptors play a large role in causing white matter damage in ischaemia, the work reviewed here shows that the role of TRP channels in glial cell function and pathology is heavily underexplored, and that a combinatorial approach to treatment during white matter pathologies may be beneficial.

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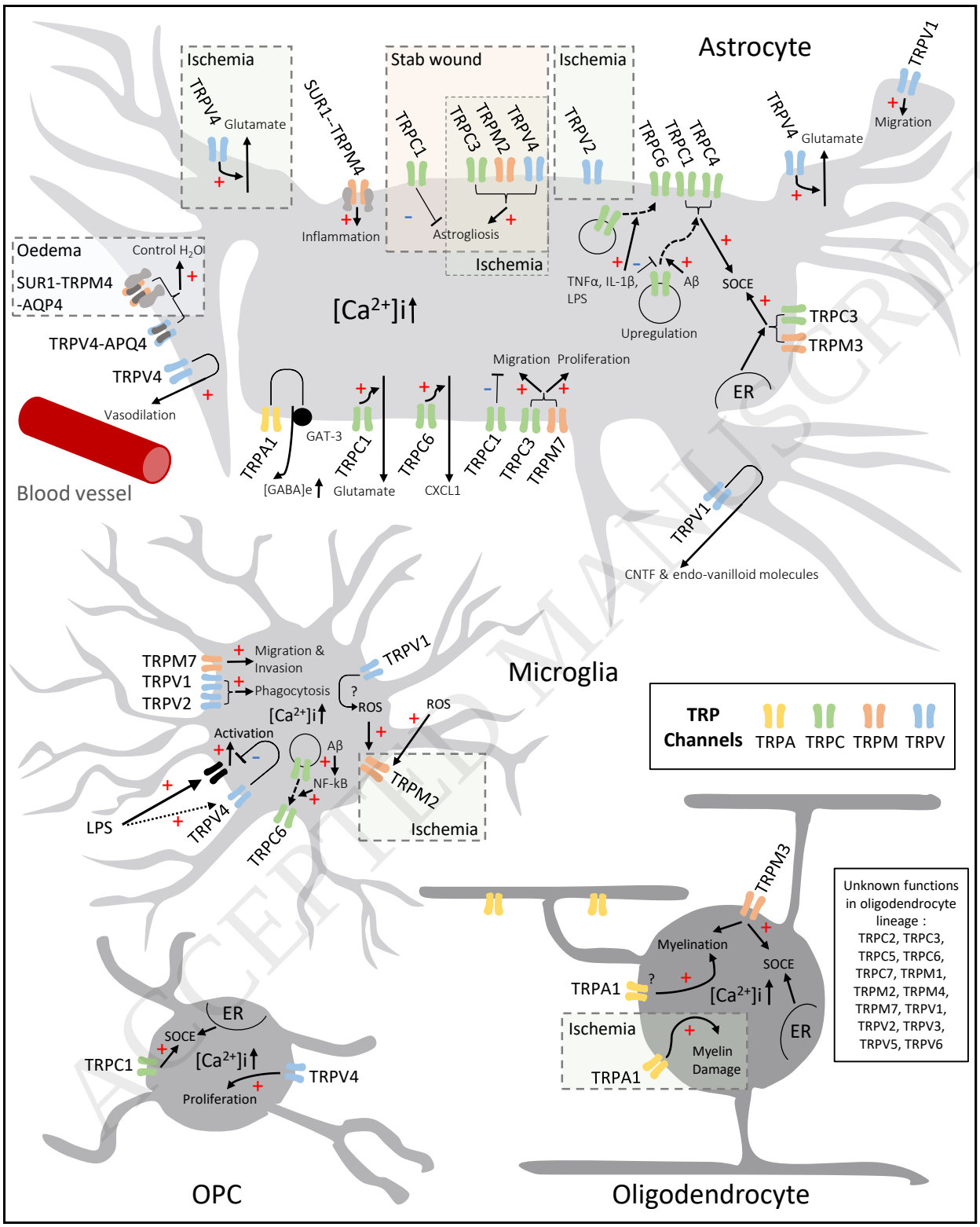
Figure 1

A schematic to illustrate the evidence for TRP channel expression in glial cells.


Astrocyte
Ischemia
TRPV4
Glutamate
SUR1–TRPM4
Inflammation
Stab wound
TRPC1
TRPC3
TRPM2
TRPV4
Astrogliosis
Ischemia
Ischemia
TRPV2
TRPC6
TRPC1
TRPC4
TNFα, IL-1β, LPS
Aβ
Upregulation
SOCE
TRPV4
Glutamate
TRPV1
Migration
Oedema
Control H_2O
SUR1-TRPM4
-AQP4
TRPV4-APQ4
TRPV4
Vasodilation
Blood vessel
[Ca2+]i
TRPC3
TRPM3
ER
Migration
Proliferation
TRPA1
GAT-3
[GABA]e
TRPC1
Glutamate
TRPC6
CXCL1
TRPC1
TRPC3
TRPM7
TRPV1
CNTF & endo-vanilloid molecules
Microglia
TRPM7
TRPV1
TRPV2
Migration & Invasion
Phagocytosis
[Ca2+]i
Activation
?
ROS
ROS
Aβ
NF-kB
LPS
TRPV4
TRPC6
TRPV1
TRPM2
Ischemia
TRP Channels
TRPA
TRPC
TRPM
TRPV
TRPM3
Myelination
SOCE
TRPA1
?
[Ca2+]i
ER
Ischemia
Myelin Damage
TRPA1
Unknown functions in oligodendrocyte lineage :
TRPC2, TRPC3, TRPC5, TRPC6, TRPC7, TRPM1, TRPM2, TRPM4, TRPM7, TRPV1, TRPV2, TRPV3, TRPV5, TRPV6
ER
SOCE
TRPC1
[Ca2+]i
TRPV4
Proliferation
OPC
Oligodendrocyte